REMARKS

Claims 1-31 are pending. Claims 1-24 have been withdrawn pursuant to a restriction requirement. Claims 25-31 and stand variously rejected under 35 U.S.C. §§ 112, 102 and 103.

By amendment herein, claims 25 and 26 have been amended for clarification of alphavirus replicon particles rather than vector particles. Support for the amendment can be found, for example, in paragraph [0041] of the specification. Claim 31 has been canceled, without prejudice or disclaimer. These claims have been amended solely to advance prosecution and these amendments should not be construed as an acknowledgment that the Examiner's position is correct. No new matter has been added as a result of these amendments and entry thereof is respectfully requested. Applicants reserve the right to file a continuation or divisional application directed to the subject matter of the original or canceled claims during the pendency of this application.

In view of the foregoing amendments and following remarks, Applicants request reconsideration of the application and withdrawal of the rejections.

Restriction Requirement

The Restriction Requirement has been deemed proper and made final. Applicants reiterate that examining Groups III through VI (class 435 and subclass 69.1) together would not be unduly burdensome and would actually save the Examiner time.

Applicants expressly reserve their right under 35 USC §121 to file one or more divisional applications directed to the nonelected subject matter during the pendency of this application.

Objections

Claims 25 and 31 were objected to due to informalities. (Office Action, page 2). By amendment herein, step (c) of claim 25 has been amended from "particle" to "particles" and to remove the term "vector." Accordingly, claim 31 now uses consistent terminology with the claim from which it depends. In view of the foregoing, Applicants submit that the objections have been obviated.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 25-31 stand rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite. (Office Action, page 3). In particular, the following issues were raised:

(1) claims 25 and 26 was alleged to be indefinite for reciting "alphavirus replicon vector particles" because the specification did not contain a clear definition of this term. (Office Action, page 3). Applicants note that the term is sufficiently clear when read in light of the specification as a whole. Nonetheless, to advance prosecution the claims have been amended to recite "alphavirus replicon particles" as described in paragraph [0041]. Accordingly, this rejection has been obviated.

(2) claim 25 was also alleged to be indefinite for failing to recite a concluding, correlative statement. By amendment herein, claim 25 now indicates that enumerating the plaques results in quantitation of the alphavirus replicon particles.

(3) claim 30 was alleged to be indefinite for failing to indicate at what step in the process agar is applied. (Office Action, page 3). Applicants note that claim 30 specifically recites that the overlaying infected cells. In other words, the claim is clear that the agar is applied following infection of step (b). Accordingly, Applicants request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

Examined claims 25-31 stand rejected as allegedly anticipated by U.S. Patent No. 5,789,245 (hereinafter "Dubensky"). (Office Action, page 4).

Applicant reminds the Examiner that, in order to be an anticipatory reference, the single reference cited by the Office must disclose each and every element of the claims. *Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). Moreover, the single source must disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). Simply put, the law requires identity as between the prior art disclosure and the invention. *See, e.g., Kalman v. Kimberly-Clark Corp.* 218 USPQ 781 (Fed. Cir. 1983), *cert. denied*, 484 US 1007 (1988).

With this legal framework in mind, Applicants note that the Office has acknowledged that Dubensky fails to describe or demonstrate elements as claimed including "the steps of infection and incubation or of overlaying infected cells with agarose." (See, Office Action, page 5). Thus, this reference fails to anticipate any of the currently pending claims.

Rejections Under 35 U.S.C. § 103

All examined claims also stand rejected as allegedly obvious over Dubensky. (Office Action, page 5). In this regard, the Office Action states that:

> *Dubensky does not specifically mention the steps of infection and incubation, or of overlaying infected cells with agarose.* However, it would have been obvious to practice Dubensky's plaque assay with the cited steps. One would have been motivated to do the specific steps because those steps defined plaque assays. It would have been obvious to apply the agar layer over the cells because plaque assays are routinely performed with an agar overlay. One of ordinary skill would know that methods of plaque assays are well-known and routinely practiced. Overlaying infected cells with agarose would have led one to reasonably expect a successful plaque assay. (Office Action, page 5, emphasis in original).

Applicants traverse the rejection and supporting remarks.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.")

Applicants submit that the Examiner has failed to make out a *prima facie* case of obviousness because Dubensky fails to teach or suggest each and every element of the invention recited in the pending claims. Further, there is simply no motivation within Dubensky to arrive at the claimed invention. Nowhere does Dubensky teach or suggest the methods of pending claims 25 to 30 -- all of which involve infecting packaging cells with alphavirus replicon particles, incubating the infected cells and enumerating the number of resulting plaques as claimed by Applicants. In fact, Dubensky teaches that plaque assays were not used in order to determine titer because it was felt these assays would not work:

> The titer of various alphavirus vector preparations, in vector units, produced from packaging cell lines such as those described in Example 7, is determined by infection of confluent monolayers of BHKSINjra-gal cells with several dilutions of vector. The titer of the vector preparation is determined at 6 hour post-infection by visualization of cells producing ß-galactosidase protein, as described above. Since the alphavirus vectors described do not contain the viral region corresponding to the structural genes, it is not possible to determine the titer of a vector preparation by plaque assay in BHK-21 cells. (See, column 124, lines 11 to 21 of Dubensky, emphasis added).

Thus, the cited reference fails to provide any motivation to arrive at the claimed methods and also fails provide the requisite reasonable expectation of success. Furthermore, contrary to the Examiner's assertions, "traditional" plaque assays were anything but routine when applied to replication-defective (replication-incompetent) alphavirus vectors as claimed by Applicants. In this regard, Applicants note that "traditional" plaque assays simply require infection of standard cells, overlay, and subsequent spread of the virus to neighboring cells. Such methods cannot be used with the claimed alphavirus replicon particles because they do not generate progeny virus (*i.e.*, because they do not encode structural proteins) and, accordingly, cannot spread from cell to cell to generate a plaque. The present invention makes use of a packaging cell line to compensate for the lack of structural protein genes in the replicon and, as such, it cannot be said that one of skill in the art would have applied "traditional" methods of plaque assays to alphavirus replicon particles as claimed.

Applicants further note that the specification as filed also details how the standard plaque assays could not be used:

> Replication defective viral vectors, such as alphavirus replicons, which are deleted of one or more genes encoding structural proteins necessary for packaging are considered "suicide vectors" and cannot spread from cell to cell. As such traditional plaque assay methods of quantitation are impossible. (See, paragraph [0061] of the specification).

Simply put, there is no basis in the reference or in the state of the art at the time of filing for making an obviousness rejection of any of the pending claims. Therefore, Appellants respectfully request that the rejection over Dubensky be withdrawn.

CONCLUSION

In view of the foregoing, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Please direct all further communications regarding this application to:

Anne S. Dollard, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097.

Respectfully submitted,

Date: 22 Oct 02

By: Pasternak
Dahna S. Pasternak
Registration No. 41,411

CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 655-8730
Facsimile: (510) 655-3542

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 25 and 26 as follow:

25. (Amended) A method for quantitating alphavirus replicon [vector] particles comprising:

a) providing a population of packaging cells;

b) contacting said packaging cells with said alphavirus replicon [vector] particles under conditions suitable and for a time sufficient for said cells to be infected with said alphavirus replicon [vector] particles;

c) incubating said infected packaging cells under conditions suitable and for a time sufficient for production of said alphavirus replicon [vector particle] particles;

d) enumerating the number of resulting plaques, thereby quantitating said alphavirus replicon particles.

26. (Amended) The method according to claim 25, wherein said packaging cells express all structural proteins necessary for packaging of said alphavirus replicon [vector] particles.

PENDING CLAIMS

1-24. Withdrawn.

25. (Amended) A method for quantitating alphavirus replicon particles comprising:

a) providing a population of packaging cells;

b) contacting said packaging cells with said alphavirus replicon particles under conditions suitable and for a time sufficient for said cells to be infected with said alphavirus replicon particles;

c) incubating said infected packaging cells under conditions suitable and for a time sufficient for production of said alphavirus replicon particles;

d) enumerating the number of resulting plaques, thereby quantitating said alphavirus replicon particles.

26. (Amended) The method according to claim 25, wherein said packaging cells express all structural proteins necessary for packaging of said alphavirus replicon particles.

27. The method according to claim 25, wherein said packaging cells comprise at least one expression cassette expressing an alphavirus capsid protein and at least one alphavirus glycoprotein.

28. The method according to claim 25, wherein said packaging cells express an alphavirus capsid protein and at least one alphavirus glycoprotein from distinct expression cassettes.

29. The method of claim 27, wherein said at least one expression cassette expresses E1 and E2 glycoproteins.

30. The method of claim 25, further comprising the step of overlaying said infected cells with a layer of agarose.

31. Canceled.